
Received Oct. 10, 1991; accepted Oct. 10, 1991. For reprints contact: Howard Sands, DuPont Merck Pharmaceutical Co., Experimental Station, P.O. Box 80328, Wilmington, DE 19880-0328.

Radiolabeled Mabs for Cancer Therapy and Diagnosis • Sands

**EDITORIAL**

Radiolabeled Monoclonal Antibodies for Cancer Therapy and Diagnosis: Is It Really a Chimera?

chi-mer-ra or chi-mae-ra n (L chimera, fr. Gk chimaira, she-goat, chimera; akin to Gk cheimon winter) 1. cap: a fire breathing she-monster in Greek mythology having a lion’s head, a goat’s body, and a serpent’s tail. 2. an illusion or fabrication of the mind, especially an unrealizable dream (1).

Considerable research over the past few years has attempted to use the high specificity and affinity of monoclonal antibodies as the basis of radiolabeled in vivo diagnosis and therapy of cancer. Results of preclinical and clinical evaluations demonstrated that these antibodies are subjected to the same physiological and metabolic processes as drugs and hormones. As a result, the tumor accumulation of these agents has been less than originally hoped (2,3). In general, uptake of the radionuclides into tumors of patients was in the range of 0.001%-0.01% of the injected dose per gram of tumor, and approximately 80% of known lesions were detected (4-6). With rare exception the limit of detection appears to be 1.0-1.5 cm (7). This limited success leads one to ask whether our hope is really a chimera, as found in definition 2 above.

One approach to increase the tumor uptake of radiolabeled antibodies, as described in the previous article by Meredith et al. (8), is the use of chimeric immunoglobulins. (see definition 1 above): most of the antibody is human with binding sites derived...
from mouse protein. This paper describes a well-designed and well-executed Phase I therapeutic study of $^{131}I$-chimeric B72.3 in patients with metastatic colorectal cancer. It is surprising to see that in this trial seven of twelve patients developed antibody to chimeric B72.3 after an initial infusion, a finding similar to that seen for murine antibodies. Most of the data reported are similar to those seen with murine antibodies: rapid whole-body clearance; inconsistent tumor localization restricted to large lesions; lack of therapeutic effects at the dose limiting bone marrow toxicity; and produce very low tumor absorbed radiation doses. The authors suggest that this construct has limited utility and offer several alternative strategies, including generation of antibodies to purified antigen such as TAG 72, other radionuclides, and chimeric human antibodies of other isotypes. The data of Meredith et al. (8) raise several important questions. First is the immunogenicity of chimeric B72.3. As they have shown, the chimeric nature of the protein is not sufficient by itself to prevent the production of human antibodies against them. Perhaps a more promising approach to the issue of immunogenicity is the production of completely human antibodies. It is encouraging that there have been no reports of human anti-human antibody (HAHA) in several clinical trials of labeled and unlabeled human antibodies, some involving several hundred patients (9–13). This is somewhat surprising since the Jerne’s idiotypic network hypothesis would predict the generation of anti-idiotypic antibodies (14). Possibly these will be seen in more detailed investigations; however, HAHA appears not to be a major limitation to the use of human antibodies for diagnosis and therapy. Unfortunately, the production of human antibodies is not without technological difficulties (15). These include: the generation of stable human cell lines; adequate antibody production; availability of suitable immune lymphocytes and good fusion partners; and low antibody affinities. Despite these limitations, labeled and unlabeled human antibodies are now available for testing in the clinic. To date, despite the lack of HAHA, radiolabeled human monoclonal IgM antibodies have not markedly improved either the selectivity or sensitivity seen in the clinic. Radioiodinated 16.88 detected tumors greater than 4 cm in six of ten patients (12). In a second study, the same antibody detected 60% of tumors greater than 2 cm but only 6% of smaller tumors. Radioiodinated 28A32, also a human IgM, detected only 31% of known lesions greater than 2 cm and failed to detect any smaller lesions (16). The large size (900K daltons) of human IgMs may be partially responsible for the lack of efficacy. The availability of human IgGs (mole wt 140K daltons) may overcome some of the limitations. Such a human protein, an IgG3(k), was reported by De Jager et al. (17). The antibody, 88BV59, recognizes an intracytoplasmic tumor associated antigen. Lesions as small as 0.5 cm were imaged and no anti-human response was detected when 88BV59 labeled with $^{99m}$Tc was used in colorectal patients. Since 88BV59 reacted moderately to strongly with 11/12 colon tumor xenografts, 17/23 primary colon tumors, 15/18 breast tumors, 10/13 ovarian tumors, 7/9 pancreatic tumors, 2/2 lung adenocarcinomas and 1/2 squamous lung carcinomas, it has the potential of being the long sought “pancanceroma” antibody (18). In addition to its potential as a carrier of radioactivity, is the possibility that as an IgG3(k), this antibody may participate in the host immune response and contribute antitumor activity. A second major question raised by the Meredith et al. paper is the reason for chimeric B72.3’s rapid clearance. Waldmann in his classic review (19) reported that the plasma half-times for radioiodinated polyclonal human IgGs and IgMs in humans were 20 hr and 5.1 days, respectively. This is in sharp contrast to what has been reported for both radioiodinated chimeric human-mouse and radioiodinated human monoclonal antibodies. The chimeric B72.3, an IgG4, had a more rapid whole-body clearance than seen in a previous report on chimeric 17-1A, an IgG1 (20). Is the difference in clearance rates due solely to the disparity in isotype, or are there differences in antibody preparation, production or glycosylation which can account for the pharmacokinetic differences seen? Studies of four human IgMs, targeted to bacterial endotoxins, cytomegalovirus, glycolipid A, or a cancer-related antigen, demonstrated a plasma half-time of approximately 20–30 hr (9–12). The reason or reasons for this disparity in clearance (5.1 days for human polyclonal IgMs versus 30 hr for human monoclonal IgMs) are unclear. Perhaps the radioiodination procedure used changed either monoclonal or polyclonal antibodies pharmacokinetics. Or perhaps a very different conclusion can be drawn from the study of naturally occurring polyclonal versus laboratory-made monoclonal antibodies resulting from factors such as differences in glycosylation. A third question is the use of “second generation antibodies,” including antibodies generated to purified antigens such as TAG 72, which express higher avidity and more rapid binding. Since there are many nonimmunological factors that control the uptake of antibody by tumor, it is not clear whether the use of second generation antibodies with increased specificity and/or avidity will, by itself, markedly change the antibody accretion. Second generation TAG 72 antibodies when tested in xenograft models showed only modest increases in tumor uptake above that of the original B72.3 (21). There are, as yet, no reports of clinical studies of these antibodies. In addition to immunological factors, several physiological factors play major roles in determining the degree of antibody accumulation. The relative permeability of the tumor vasculature is a major determinant in the uptake of radioiodinated antibody by tumor (22). Lack of lym-
phatic drainage leads to an increase in the interstitial pressure found in tumors; this in turn leads to the collapse of the small capillaries and aberrant blood flow (22). Reduced fluid flow rates, due to the increased pressure, combined with the slow diffusion rate of macromolecules, produces slow migration rates for antibodies. An IgG will take 2–3 days to move 1 mm, while it will take 0.5–1 day for a Fab to migrate the same distance (24). The slow migration rate combined with high interstitial pressure results in a reduced tumor accretion of antibody, which will not be overcome simply by increasing antibody specificity and/or affinity.

An alternative approach to murine and human monoclonal antibodies is the single chain binding protein. This protein is considerably smaller than a Fab antibody fragment and possesses antigen binding ability. A combinator single chain protein having tumor targeting ability has been reported by Colcher et al. (25). This protein, when radiiodinated, demonstrated more rapid blood clearance than a Fab, yet maintained a high degree of specific tumor localization relative to retention in blood and normal tissue. Unfortunately, because of its rapid clearance, its absolute tumor uptake in tumor xenografts was much lower than that seen with murine IgGs and Fabs. Since single-chain binding proteins are smaller molecular entities, methods may be found to modify the protein to tailor its biodistribution and pharmacokinetics to suit the clinical needs.

Finally, the suggestion by Meredith et al. for research into other radiouclides is of value. Nonspecific uptake and catabolism of radiolabeled antibodies lead to rapid clearance and increased nontarget organ uptake and, in therapeutic applications, toxicity. This phenomenon is determined not only by the nature of the targeting molecule, but by its radiouclide and conjugation chemistry. For example, uptake of the radiiodinated IgG by liver hepatocytes is similar to that of radio-iodium labeled IgG, but retention time due to catabolism of the protein and trapping of the radionuclides differ greatly (26). Other radionuclides and/or different chelation chemistries may result in improved diagnostics and therapeutics. At this time, we cannot answer the original question: is the concept of the use of radiolabeled monoclonal antibodies for cancer diagnosis and therapy a chimera, "an illusion or fabrication of the mind, especially an unrealizable dream." While the results from initial clinical trials have not lived up to our earlier expectations, we now have a better understanding of the problems that need to be solved. Improved immunological reagents (e.g., human IgGs, single-chain binding proteins, etc.) and better chelation chemistry combined with a greater knowledge of tumor physiology (vascularity, pressure and permeability, interstitial pressure, non-target antibody uptake and catabolism) should eventually make the dream a reality. We have just started to approach these problems and should be able to overcome them with combined efforts in chemical, physiological and immunological research. The result will be that the high specificity and affinity of monoclonal antibodies will eventually serve as the basis of in vivo radioisotopic diagnosis and therapy of cancer.

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REFERENCES

FIRST IMPRESSIONS

PURPOSE
Twenty-four-hour postoperative evaluation of right pelvic renal transplant in a 43-yr-old female. Foley catheter is in place.

TRACER
99mTc-MAG3, 5.4 mCi

ROUTE OF ADMINISTRATION
Intravenous

TIME AFTER INJECTION
30 min

INSTRUMENTATION
GE Maxicam/Star

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